REMARKS

Claim Amendments

New dependent method of treatment claims have been added by the above amendments. Specifically:

New claim 15 is dependent on claim 3 or claim 4, and further defines the cancer as a non-small cell lung cancer (NSCLC). Support for this claim is found in the specification, *inter alia*, at page 14, lines 10-13.

New claim 16 is dependent on claim 5 or claim 6, and further defines the tumour as a tumour of the colon, breast, prostate, lungs or skin. Support for this claim is found in the specification, *inter alia*, at page 14, lines 8-10.

Claim Rejections - 35 USC § 103

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin et al (WO 01/32651) in view Magne *et al.* This ground for rejection is respectfully traversed.

The Examiner notes that claims 1-6 are drawn to a method for the treatment of cancer and a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, which comprises administering ZD6474 and ZD1839, optionally with an effective amount of ionizing radiation, and that claims 7 and 8 are drawn to a pharmaceutical composition and kit comprising ZD6474 and ZD1839.

In formulating this rejection, the Examiner asserts that Hennequin *et al.* discloses a method for the treatment of cancer (in particular solid tumors, citing page 28, lines 11-17), and a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal (citing page 26, lines 10-14), which method comprises administering a compound of formula I as generically described beginning on page 3 of the reference. The Examiner further notes that ZD6474 is specifically identified as a compound of Formula I (citing claim 8). The Examiner then notes that this treatment may additionally include radiotherapy administered simultaneously, sequentially or separately, citing page 26, lines 22-30 of this reference. The Examiner acknowledges, however, that Hennequin *et al.* does not teach this method of treatment further comprising the administration of ZD1839.

Thus Magne *et al.* is cited as teaching that ZD1839 (Iressa) enhances the growth inhibitory effect of other cytotoxic drugs (citing page 825, second column), and as further teaching that ZD1839 is a strong radiosensitizer as well as chemosensitizer (citing page 826, first column).

From these observations the Examiner concludes:

> Therefore it would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add the step of administrating ZD1839 to the method of treatment described in Hennequin et al, because of its known chemosensitizing and radiosensitizing activity, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

(Action at page 3).

This ground for rejection is respectfully traversed.

At page 3 of the present disclosure Applicants specifically acknowledge the disclosure on page 26 of Hennequin *et al.* (WO 01/32651), now cited by the Examiner, noting that:

> In WO 01/32651 it is stated that compounds of that invention: "may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment."

WO 01/32651 describe examples of such conjoint treatment including surgery, radiotherapy and chemotherapy. In fact WO 01/32651 expands upon the conjoint chemotherapy treatment, describing at page 27 five main categories of therapeutic agent as follows:

> (i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate));
>
> (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide, abarelix), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase

plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

(WO 01/32651, page 27, lines 1-30).

The compound that is ZD6474 is just one of a number of compounds that are within the scope of the WO 01/32651 disclosure or described therein, and radiotherapy is just one of the many possible described conjoint treatments that can be used with any of such compounds. The above-quoted subparagraph (ii) *generally mentions* tyrosine kinase inhibitors as *one of the many* cytostatic agents that can be used in the conjoint treatments, but there is no specific mention of ZD1839 or disclosure that would lead to ZD1839 in particular. It is therefore respectfully submitted that there is nothing in WO 01/32651 that would support any assertion of *prima facie* obviousness of the present claims, and it is understood that the Examiner does not make such an assertion.

Rather, the Examiner additionally cites Magne *et al.*, which is said to teach that ZD1839 enhances the growth inhibitory effect of other cytotoxic drugs (citing page 825, second column), and that ZD1839 is a strong radiosensitizer as well as chemosensitizer (page 826, first column). However, what Magne *et al.* actually states with respect to ZD1839 and other cytotoxic drugs is:

> The antiproliferative activity of ZD1839 combined with a number of cytotoxic drugs (cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, doxorubibin, etoposide, topotecan and raltitrexed) has been recently assessed in a variety of human cancer cell lines (Ciardiello et al, 2000; Sirotnak et al, 2000). The co-administration of ZD1839 was found to enhance the growth-inhibitory effects of all cytotoxic drugs tested.

(Magne *et al.*, pages 825-26; emphasis added). The comment on ZD1839 being a "strong radio- and chemosensitizer" is also with reference to these same conventional cytotoxic drugs and also includes the authors' own work reported in the reference with respect to cisplatin, 5-fluorouracil (5-FU) and radiation. However, the presently claimed invention is *not* directed toward the conjoint treatment with ZD1839 with *conventional* cytotoxic drugs. The present application relates to the combination of ZD1839 with a very particular anti-cancer agent, ZD6474, which targets the tumour vasculature. This is a very different activity to the conventional cytotoxic drugs mentioned in Magne *et al.*

It is therefore respectfully submitted that neither WO 01/32651 nor Magne *et al.* provide any teaching, suggestion or motivation for combining ZD1839 with an agent that targets the tumour vasculature, no less ZD6474 in particular.

With respect to composition claim 7 and kit claim 8, the Examiner reminds Applicant of *In re Kerkhoven*, which is said to affirm that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Kerkhoven involved a process for combining known anionic and known nonionic detergents, where applicant acknowledged that the detergent-making art often prefers such anionic-nonionic mixtures. The Examiner seems to be extrapolating this to the pharmaceutical arts and expansively asserting that it is *prima facie* obvious to combine *an agent* used in the treatment of cancer with *any other agent* used in the treatment of cancer, regardless of their nature or mode of operation.

Nevertheless, it is respectfully submitted that *even if Kerkhoven* is so expansively applied, any *prima facie* obviousness that might thereby arise has been overcome by the unexpected and surprising results demonstrated by the comparative evidence presented in the present application.

Nowhere in WO 01/32651 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects, whereas it is stated at page 3, lines 16-23 of the present application that "[u]nexpectedly and surprisingly we have now found that the particular compound ZD6474 used in combination with a particular selection from the broad description of combination therapies listed in WO 98/13354 and WO 01/32651, namely with ZD1839, produces significantly better effects than any one of ZD6474 and ZD1839 used alone," and that in particular, "ZD6474 used in combination with ZD1839 produces significantly better effects on solid tumours than any one of ZD6474 and ZD1839 used alone."

This surprising beneficial result is demonstrated by the comparative data present at pages 17-19 of the present specification. The Examiner's attention is drawn in particular to the comparative data presented on the table at page 17 which is graphically shown in Figure 1, and the comparative data presented on the table at page 18 which is graphically shown in Figure 2.

Conclusion

The above observations show that the applied references, when they are considered as a whole for what they would actually teach the skilled person, do not render the presently claimed invention *prima facie* obvious, but *even if* they did, any such *prima facie* obviousness is overcome by the comparative evidence of unexpected beneficial results specifically presented in the specification. Accordingly, it is believed that this rejection has been overcome, and it is respectfully requested that this rejection be withdrawn and that all claims be allowed.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required

extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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Date: **April 15, 2008** By: _____

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